

WHAT IS CLAIMED IS:

General tiling claims

1 1. An array of oligonucleotide probes immobilized on a
2 solid support, the array comprising at least two sets of
3 oligonucleotide probes,

4 (1) a first probe set comprising a plurality of
5 probes, each probe comprising a segment of at least three
6 nucleotides exactly complementary to a subsequence of the
7 reference sequence, the segment including at least one
8 interrogation position complementary to a corresponding
9 nucleotide in the reference sequence,

10 (2) a second probe set comprising a corresponding
11 probe for each probe in the first probe set, the corresponding
12 probe in the second probe set being identical to a sequence
13 comprising the corresponding probe from the first probe set or
14 a subsequence of at least three nucleotides thereof that
15 includes the at least one interrogation position, except that
16 the at least one interrogation position is occupied by a
17 different nucleotide in each of the two corresponding probes
18 from the first and second probe sets;

19 wherein the probes in the first probe set have at least
20 two interrogation positions respectively corresponding to each
21 of two contiguous nucleotides in the reference sequence.

1 2. An array of oligonucleotide probes immobilized on a
2 solid support, the array comprising at least four sets of
3 oligonucleotide probes,

4 (1) a first probe set comprising a plurality of
5 probes, each probe comprising a segment of at least three
6 nucleotides exactly complementary to a subsequence of the
7 reference sequence, the segment including at least one
8 interrogation position complementary to a corresponding
9 nucleotide in the reference sequence,

10 (2) second, third and fourth probe sets, each
11 comprising a corresponding probe for each probe in the first
12 probe set, the probes in the second, third and fourth probe
13 sets being identical to a sequence comprising the
14 corresponding probe from the first probe set or a subsequence

15 of at least three nucleotides thereof that includes the at
16 least one interrogation position, except that the at least one
17 interrogation position is occupied by a different nucleotide
18 in each of the four corresponding probes from the four probe
19 sets.

1 3. The oligonucleotide array of claim 2, further
2 comprising a fifth probe set comprising a corresponding probe
3 for each probe in the first probe set, the corresponding probe
4 from the fifth probe set being identical to a sequence
5 comprising the corresponding probe from the first probe set or
6 a subsequence of at least three nucleotides thereof that
7 includes the at least one interrogation position, except that
8 the at least one interrogation position is deleted in the
9 corresponding probe from the fifth probe set.

1 4. The oligonucleotide array of claim 2, further
2 comprising a sixth probe set comprising a corresponding probe
3 for each probe in the first probe set, the corresponding probe
4 from the sixth probe set being identical to a sequence
5 comprising the corresponding probe from the first probe set or
6 a subsequence of at least three nucleotides thereof that
7 includes the at least one interrogation position, except that
8 an additional nucleotide is inserted adjacent to the at least
9 one interrogation position in the corresponding probe from the
10 first probe set.

1 5. The array of claim 2, wherein the first probe set has
2 at least three interrogation positions respectively
3 corresponding to each of three contiguous nucleotides in a
4 reference sequence.

1 6. The array of claim 2, wherein the first probe set has
2 at least 50 interrogation positions respectively corresponding
3 to each of 50 contiguous nucleotides in a reference sequence.

1 7. The array of claim 1 or 2, wherein the first probe
2 set has at least 100 interrogation positions respectively

3 corresponding to each of 100 contiguous nucleotides in a
4 reference sequence.

1 8. The oligonucleotide array of claim 1 or 2, wherein
2 the first probe set has an interrogation position
3 corresponding to each of at least 30% of the nucleotides in a
4 reference sequence and the reference sequence comprises at
5 least 100 nucleotides.

1 9. The oligonucleotide array of claim 8, wherein the
2 first probe set comprises probes which completely span the
3 reference sequence, which probes relative to the reference
4 sequence, overlap one another in sequence.

1 10. The oligonucleotide array of claim 9, wherein the
2 first probe set has an interrogation position corresponding to
3 each of the nucleotides in the reference sequence.

1 11. The oligonucleotide array of claim 10, wherein the
2 probes are oligodeoxyribonucleotides.

1 12. The oligonucleotide array of claim 1 or 2, wherein
2 the array comprises between 100 and 10,000 probes.

1 13. The oligonucleotide array of claim 1 or 2, wherein
2 the array comprises between 10,000 and 100,000 probes.

1 14. The oligonucleotide array of claim 1 or 2, wherein
2 the array comprises between 100,000 and 10,000,000 probes.

1 15. The oligonucleotide array of claim 1 or 2, wherein
2 the probes are linked to the support via a spacer.

1 16. The oligonucleotide array of claim 1 or 2, wherein
2 the segment in each probe of the first probe set that is
3 exactly complementary to the subsequence of the reference
4 sequence is 9-21 nucleotides.

1 17. The oligonucleotide array of claim 16, wherein the
2 segment is n nucleotides long, and the subsequence is at least
3 n-2 nucleotides long.

1 18. The oligonucleotide array of claim 1 or 2, wherein
2 each probe of the first probe set consists of the segment that
3 is exactly complementary to the subsequence of the reference
4 sequence.

1 19. The oligonucleotide array of claim 1 or 2, wherein
2 the probes in the second, third and fourth probe sets are
3 identical to the corresponding probe from the first probe set
4 except that the at least one interrogation position is
5 occupied by a different nucleotide in each of the four
6 corresponding probes from the four probe sets.

1 20. The array of claim 2, further comprising fifth,
2 sixth and seventh probe sets, wherein:
3 the segment of each probe in the first set
4 includes at least two interrogation positions each
5 corresponding to a nucleotide in the reference sequence,
6 the second, third and fourth probe sets, each
7 comprise a corresponding probe for each probe in the first
8 probe set, the corresponding probes in the second, third and
9 fourth probe sets being identical to a sequence comprising the
10 corresponding probe from the first probe set or a subsequence
11 of at least three nucleotides thereof that includes a first
12 interrogation position except that the first interrogation
13 position is occupied by a different nucleotide in each of the
14 four corresponding probes from the four probe sets;
15 the fifth, sixth and seventh probe sets, each
16 comprising a corresponding probe for each probe in the first
17 probe set, the probes in the fifth, sixth and seventh probe
18 sets being identical to a sequence comprising the
19 corresponding probe from the first probe set or a subsequence
20 of at least three nucleotides thereof that includes a second
21 interrogation position, except that the second interrogation

22 position is occupied by a different nucleotide in each of the
23 four corresponding probes from the four probe sets.

1 21. The array of claim 2, wherein each probe in the
2 first probe set further comprises a second segment of at least
3 three nucleotides exactly complementary to a second
4 subsequence of the reference sequence, and the probes from the
5 second, third and fourth probe sets comprise the corresponding
6 probe from the first probe set or a subsequence thereof
7 comprising the first and second segments except in the at
8 least one interrogation position.

1 22. The array of claim 2, further comprising:
2 a fifth probe set comprising at least one probe
3 comprising a segment of at least seven nucleotides exactly
4 complementary to a subsequence of the reference sequence
5 except at one or two positions, the segment including at least
6 one interrogation position corresponding to a nucleotide in
7 the reference sequence not at the one or two positions;
8 sixth, seventh and eighth probe sets, each comprising a
9 probe for each probe in the fifth probe set, the corresponding
10 probes from the sixth, seventh & eighth probe sets being
11 identical to a sequence comprising the corresponding probe
12 from the fifth probe set or a subsequence of at least nine
13 nucleotides thereof including the at least one interrogation
14 position and the one or two positions, except in the at least
15 one interrogation position, which is occupied by a different
16 nucleotide in each of the four probes.

1 23. The array of claim 2, wherein the probes are
2 arranged on the substrate so that the first set of probes is
3 arranged in a row across the substrate in an order reflecting
4 the overlap between the probes and the reference sequence, and
5 the additional sets of probes are arranged in columns relative
6 to the probes in said first set, so that probes with the same
7 interrogation position are in the same column and so that each
8 column comprises at least 4 probes.

1 24. The array of Claim 2, wherein said probes are 12 to
2 17 nucleotides in length.

1 25. The array of Claim 2, wherein said probes are 15
2 nucleotides in length and attached by a covalent linkage to a
3 site on a 3'-end of said probes, and said interrogation
4 position is located at position 7, relative to the 3'-end of
5 said probes.

1 26. The array of claim 2, further comprises fifth,
2 sixth, seventh and eighth probe sets,

3 (1) a fifth probe set comprising a plurality of
4 probes, each probe comprising a segment of at least three
5 nucleotides exactly complementary to a subsequence of a second
6 reference sequence, the segment including at least one
7 interrogation position complementary to a corresponding
8 nucleotide in the reference sequence,

9 (2) the sixth, seventh, and eighth probe sets, each
10 comprising a corresponding probe for each probe in the fifth
11 probe set, the probes in the sixth, seventh and eighth probe
12 sets being identical to a sequence comprising the
13 corresponding probe from the fifth probe set or a subsequence
14 of at least three nucleotides thereof that includes the at
15 least one interrogation position, except that the at least one
16 interrogation position is occupied by a different nucleotide
17 in each of the four corresponding probes from the fifth,
18 sixth, seventh and eighth probe sets.

1 27. The array of claim 22, wherein the first, second,
2 third and fourth probe sets have probes of a first length and
3 the fifth, sixth, seventh and eighth probe sets have probes of
4 a second length different from the first length.

Tiling for wildtype and mutant reference sequences

1 28. An array of oligonucleotide probes immobilized on a
2 solid support, the array comprising at least one pair of first
3 and second probe groups, each group comprising a first and
4 second sets of oligonucleotide probes as defined by claim 1;

5 wherein each probe in the first probe set from the
6 first group is exactly complementary to a subsequence of a
7 first reference sequence and each probe in the first probe set
8 from the second group is exactly complementary to a
9 subsequence from a second reference sequence.

1 29. The array of claim 28, wherein the second reference
2 sequence is a mutated form of the first reference sequence.

1 30. The array of claim 28, wherein each group further
2 comprises third and fourth probe sets, each comprising a
3 corresponding probe for each probe in the first probe set, the
4 probes in the second, third and fourth probe sets being
5 identical to a sequence comprising the corresponding probe
6 from the first probe set or a subsequence of at least three
7 nucleotides thereof that includes the interrogation position,
8 except that the interrogation position is occupied by a
9 different nucleotide in each of the four corresponding probes
10 from the four probe sets.

1 31. The array of claim 30 that comprises at least five
2 pairs of first and second probe groups, wherein the probes in
3 the first probe sets from the first groups of the five pairs
4 are exactly complementary to subsequences from five different
5 respective first reference sequences.

1 32. The array of claim 30 that comprises at least forty
2 pairs of first and second probe groups, wherein the probes in
3 the first probe sets from the first groups of the forty pairs
4 are exactly complementary to subsequences from forty
5 respective first reference sequences.

Block tiling

1 33. An array of oligonucleotide probes immobilized on a
2 solid support, the array comprising at least a group of probes
3 comprising:

4 a wildtype probe comprising a segment of at least three
5 nucleotides exactly complementary to a subsequence of a

6 reference sequence, the segment having at least first and
7 second interrogation positions corresponding to first and
8 second nucleotides in the reference sequence,

9 a first set of three mutant probes, each identical to a
10 sequence comprising the wildtype probe or a subsequence of at
11 least three nucleotides thereof including the first and second
12 interrogation positions, except in the first interrogation
13 position, which is occupied by a different nucleotide in each
14 of the three mutant probes and the wildtype probe;

15 a second set of three mutant probes, each identical to a
16 sequence comprising the wildtype probe or a subsequence of at
17 least three nucleotides thereof including the first and second
18 interrogation positions, except in the second interrogation
19 position, which is occupied by a different nucleotide in each
20 of the three mutant probes and the wildtype probe.

1 34. The array of claim 33, wherein the segment of the
2 wildtype probe comprises 3-20 interrogation positions
3 corresponding to 3-20 respective nucleotides in the reference
4 sequence, and the array comprises 3-20 respective sets of
5 three mutant probes, each of the three probes identical to a
6 sequence comprising the wildtype probe or a subsequence
7 thereof including the 3-20 interrogation positions, except
8 that one of the 3-20 interrogation positions is occupied by a
9 different nucleotide in each of the three mutant probes and
10 the wildtype probes, the one of the 3-20 interrogation
11 positions being different in each of the 3-20 respective sets
12 of three mutant probes.

1 35. An array of probes immobilized to a solid support
2 comprising two groups of probes, each group as defined by
3 claim 33, a first group comprising a wildtype probe comprising
4 a segment exactly complementary to a subsequence of a first
5 reference sequence and a second group comprising a wildtype
6 probe comprising a segment exactly complementary to a
7 subsequence of a second reference sequence.

1 36. The array of claim 35, comprising at least 10-100
2 groups of probes, each comprising a wildtype probe comprising
3 a segment exactly complementary to a subsequence of at least
4 10-100 respective reference sequences.

Pooled probes

1 37. A method of comparing a target sequence with a
2 reference sequence, the method comprising:
3 identifying variants of a reference sequence differing
4 from the reference sequence in at least one nucleotide;
5 assigning each variant a designation,
6 providing an array of pools of probes, each pool
7 occupying a separate cell of the array, wherein each pool
8 comprises a probe comprising a segment exactly complementary
9 to each variant sequence assigned a particular designation,
10 contacting the array with a target sequence comprising a
11 variant of the reference sequence;
12 determining the relative hybridization intensities of the
13 pools in the array to the target sequence;
14 determining the target sequence from the relative
15 hybridization intensities of the pools.

1 38. The method of claim 37, wherein the variants are
2 assigned numbers according to an error code.

1 39. The method of claim 37, wherein each variant is
2 assigned a designation having at least one digit and at least
3 one value for the digit, and each pool comprise a probe
4 comprising a segment exactly complementary to each variant
5 sequence assigned a particular value in a particular digit.

1 40. The method of claim 39, wherein the variants are
2 assigned successive numbers in a numbering system of base m
3 having n digits, and the array comprises $n \times (m-1)$ pools of
4 probes.

1 41. The method of claim 40, wherein each pool further
2 comprises a probe comprising a segment exactly complementary
3 to the reference sequence.

: **Trellis tiling**

1 42. A pooled probe comprising a segment exactly
2 complementary to a subsequence of a reference sequence except
3 at a first interrogation position occupied by a pooled
4 nucleotide N, a second interrogation position occupied by a
5 pooled nucleotide selected from the group of three consisting
6 of (1) M or K, (2) R or Y and (3) S or W, and a third
7 interrogation position occupied by a second pooled nucleotide
8 selected from the group, wherein the pooled nucleotide
9 occupying the second interrogation position comprises a
10 nucleotide complementary to a corresponding nucleotide from
11 the reference sequence when the second pooled probe and
12 reference sequence are maximally aligned, and the pooled
13 nucleotide occupying the third interrogation position
14 comprises a nucleotide complementary to a corresponding
15 nucleotide from the reference sequence when the third pooled
16 probe and the reference sequence are maximally aligned,
17 wherein N is A, C, G or T(U), K is G or T(U), M is A or C, R
18 is A or G, Y is C or T(U), W is A or T(U) and S is G or C.

1 43. An array of oligonucleotide probes immobilized on
2 solid support, the array comprising:

3 first, second and third cells respectively occupied by
4 first, second and third pooled probes, each pooled probe
5 comprising a segment exactly complementary to a subsequence of
6 a reference sequence except at a first interrogation position
7 occupied by a pooled nucleotide N, a second interrogation
8 position occupied by a pooled nucleotide selected from the
9 group of three consisting of (1) M or K, (2) R or Y and (3) S
10 or W, and a third interrogation position occupied by a second
11 pooled nucleotide selected from the group, wherein the pooled
12 nucleotide occupying the second interrogation position
13 comprises a nucleotide complementary to a corresponding
14 nucleotide from the reference sequence when the pooled probe

15 and the reference sequence are maximally aligned, and the
16 pooled nucleotide occupying the third interrogation position
17 comprises a nucleotide complementary to a corresponding
18 nucleotide from the reference sequence when the pooled probe
19 and the reference sequence are maximally aligned;
20 provided that one of the three interrogation
21 positions in the each of the three pooled probes is aligned
22 with the same corresponding nucleotide in the reference
23 sequence, this interrogation position being occupied by an N
24 in one of the pooled probes, and a different pooled nucleotide
25 in each of the other two pooled probes,
26 wherein N is A, C, G or T(U), K is G or T(U), M is A
27 or C, R is A or G, Y is C or T(U), W is A or T(U) and S is G
28 or C.

1 44. The array of claim 43 further comprising:
2 fourth and fifth cells respectively occupied by fourth
3 and fifth pooled probes, each pooled probe as defined by
4 claim 43,
5 wherein one of the three interrogation position in the
6 second, third and fourth pooled probes is aligned with the
7 same corresponding nucleotide in the reference sequence, this
8 interrogation position being occupied by an N in one of the
9 pooled probes, and a different pooled nucleotide in each of
10 the other two pooled probes,
11 wherein one of the three interrogation position in the
12 third, fourth and fifth pooled probes is aligned with the same
13 corresponding nucleotide in the reference sequence, this
14 interrogation position being occupied by an N in one of the
15 pooled probes, and a different pooled nucleotide in each of
16 the other two pooled probes.

1 45. The array of claim 44, wherein the pooled probes are
2 identical except at the interrogation positions.

1 46. The array of claim 44, wherein the first, second,
2 third, fourth and fifth pooled probes are exactly
3 complementary to five respective subsequences of the reference

4 sequences that from each other by increments of one
5 nucleotide.

Bridge tiling

1 47. An array of oligonucleotide probes immobilized on a
2 solid support, the array comprising at least four probes:
3 a first probe comprising first and second segments, each
4 of at least three nucleotides and exactly complementary to
5 first and second subsequences of a reference sequences, the
6 segments including at least one interrogation position
7 corresponding to a nucleotide in the reference sequence,
8 wherein either (1) the first and second subsequences are
9 noncontiguous, or (2) the first and second subsequences are
10 contiguous and the first and second segments are inverted
11 relative to the complement of the first and second
12 subsequences in the reference sequence;
13 second, third and fourth probes, identical to a sequence
14 comprising the first probe or a subsequence thereof comprising
15 at least three nucleotides from each of the first and second
16 segments, except in the at least one interrogation position,
17 which differs in each of the probes.

1 48. The array of claim 47, wherein the first and second
2 subsequences are separated by one or two nucleotides in the
3 reference sequence.

Two interrogation positions (no wildtype)

1 49. An array of oligonucleotide probes immobilized on a
2 solid support, the array comprising at least a set of four
3 probes, each of the probes comprising a segment of at least 7
4 nucleotides that is exactly complementary to a subsequence
5 from a reference sequence, except that the segment may or may
6 not be exactly complementary at two interrogation positions,
7 wherein:
8 the first interrogation position is occupied by a
9 different nucleotide in each of the four probes,
10 the second interrogation position is occupied by a
11 different nucleotide in each of the four probes,

12 in first and second probes, the segment is exactly
13 complementary to the subsequence, except at not more than one
14 of the interrogation positions, and

15 in third and fourth probes, the segment is exactly
16 complementary to the subsequence, except at both of the
17 interrogation positions.

1 50. An array of probes immobilized to a support, the
2 array comprising at least 100 sets of 4 probes, each set as
3 defined by claim 49, the probes from the at least 100 sets
4 comprising at least 100 respective segments, the segments
5 having at least 100 respective first and second interrogation
6 positions.

Helper mutations

1 51. An array of oligonucleotide probes immobilized on a
2 solid support, the array comprising a set of probes
3 comprising:

4 a first probe comprising a segment of at least 7
5 nucleotides exactly complementary to a subsequence of a
6 reference sequence except at one or two positions, the segment
7 including an interrogation position not at the one or two
8 positions;

9 second, third and fourth mutant probes, each identical to
10 a sequence comprising the wildtype probe or a subsequence
11 thereof including the interrogation position and the one or
12 two positions, except in the interrogation position, which is
13 occupied by a different nucleotide in each of the four probes.

Omission of Perfectly Matched Probe

1 52. An array of oligonucleotide probes immobilized on a
2 solid support, the array comprising at least two sets of
3 oligonucleotide probes,

4 (1) a first probe set comprising a plurality of
5 probes, each probe comprising a segment exactly complementary
6 to a subsequence of at least 3 nucleotides of a reference
7 sequence except at an interrogation position,

8 (2) a second probe set comprising a corresponding
9 probe for each probe in the first probe set, the corresponding
10 probe in the second probe set being identical to a sequence
11 comprising the corresponding probe from the first probe set or
12 a subsequence of at least three nucleotides thereof that
13 includes the interrogation position, except that the
14 interrogation position is occupied by a different nucleotide
15 in each of the two corresponding probes and the complement to
16 the reference sequence,

17 wherein the probes in the first probe set have at
18 least three interrogation positions respectively corresponding
19 to each of three contiguous nucleotides in the reference
20 sequence.

Methods

1 53. A method of comparing a target nucleic acid with a
2 reference sequence comprising a predetermined sequence of
3 nucleotides, the method comprising:

4 (a) hybridizing the target nucleic acid to an array
5 of oligonucleotide probes immobilized on a solid support, the
6 array comprising:

7 (1) a first probe set comprising a plurality of
8 probes, each probe comprising a segment of at least three
9 nucleotides exactly complementary to a subsequence of the
10 reference sequence, the segment including at least one
11 interrogation position complementary to a corresponding
12 nucleotide in the reference sequence,

13 (2) a second probe set comprising a corresponding
14 probe for each probe in the first probe set, the corresponding
15 probe in the second probe set being identical to a sequence
16 comprising the corresponding probe from the first probe set or
17 a subsequence of at least three nucleotides thereof that
18 includes the at least one interrogation position, except that
19 the at least one interrogation position is occupied by a
20 different nucleotide in each of the two corresponding probes
21 from the first and second probe sets;

22 wherein, the probes in the first probe set have at
23 least three interrogation positions respectively corresponding

24 to each of at least three nucleotides in the reference
25 sequence, and
26 (b) determining which probes, relative to one
27 another, in the array bind specifically to the target nucleic
28 acid, the relative specific binding of the probes indicating
29 whether the target sequence is the same or different from the
30 reference sequence.

1 54. The method of claim 53, wherein the array further
2 comprises third and fourth probe sets, each comprising a
3 corresponding probe for each probe in the first probe set, the
4 probes in the second, third and fourth probe sets being
5 identical to a sequence comprising the corresponding probe
6 from the first probe set or a subsequence of at least three
7 nucleotides thereof that includes the at least one
8 interrogation position, except that the at least one
9 interrogation position is occupied by a different nucleotide
10 in each of the four corresponding probes from the four probe
11 sets.

1 55. The method of claim 54, wherein the target sequence
2 has a substituted nucleotide relative to the reference
3 sequence in at least one undetermined position, and the
4 relative specific binding of the probes indicates the location
5 of the position and the nucleotide occupying the position in
6 the target sequence.

1 56. The method of claim 54, wherein:
2 the hybridizing step comprises hybridizing the
3 target nucleic acid and a second target nucleic acid to the
4 array; and
5 the determining step comprises determining which
6 probes, relative to one another, in the array bind
7 specifically to the target nucleic acid or the second target
8 nucleic acid, the relative specific binding of the probes
9 indicating whether the target sequence is the same or
10 different from the reference sequence and whether the second

11 target sequence is the same or different from the reference
12 sequence.

1 57. The method of claim 56, wherein the target sequence
2 has a label and the second target sequence has a second label
3 different from the label.

1 58. The method of claim 56, wherein undetermined first
2 and second proportions of the first and second target
3 sequences are hybridized to the array and the specific binding
4 indicates the proportions.

1 59. The method of claim 54, further comprising:
2 (c) removing the target nucleic acid from the array;
3 (d) hybridizing a second target nucleic acid to the
4 array;
5 (e) determining which probes, relative to one another, in
6 the array bind specifically to the second target nucleic acid,
7 the relative specific binding of the probes indicating whether
8 the second target sequence is the same or different from the
9 reference sequence.

1 60. A method of comparing a target nucleic acid with a
2 reference sequence comprising a predetermined sequence of
3 nucleotides, the method comprising:
4 hybridizing the target sequence to the array of
5 claim 28;
6 determining which probes in the first group,
7 relative to one another, hybridize to the target sequence, the
8 relative specific binding of the probes indicating whether the
9 target sequence is the same or different from the first
10 reference sequence;
11 determining which probes in the second group,
12 relative to one another, hybridize to the target sequence, the
13 relative specific binding of the probes indicating whether the
14 target sequence is the same or different from the second
15 reference sequence.

1 61. The method of claim 60, wherein the hybridizing step
2 comprising hybridizing the target sequence and a second target
3 sequence to the array, and the relative specific binding of
4 the probes from the first group indicates that the target is
5 identical to the first reference sequence, and the relative
6 specific binding of the probes from the second group indicates
7 that the second target sequence is identical to the second
8 reference sequence.

1 62. The method of claim 61, wherein the first and second
2 target sequences are heterozygous alleles of a gene.

Comparative hybridization

1 63. A method of comparing a target nucleic acid with a
2 reference sequence comprising a predetermined sequence of
3 nucleotides, the method comprising:
4 (a) hybridizing the reference sequence to an array
5 of oligonucleotide probes immobilized on a solid support, the
6 array comprising;
7 (1) a first probe set comprising a plurality of
8 probes, each probe comprising a segment of at least 3
9 nucleotides exactly complementary to a subsequence of the
10 reference sequence except in at least one interrogation
11 position;
12 (2) a second probe set comprising a corresponding
13 probe for each probe in the first probe set, the corresponding
14 probe in the second probe set being identical to a sequence
15 comprising the corresponding probe from the first probe set or
16 a subsequence of at least three nucleotides thereof that
17 includes the at least one interrogation position, except that
18 the at least one interrogation position is occupied by a
19 different nucleotide in each of the two corresponding probes
20 from the first and second probe sets; and
21 (b) determining which probes, relative to one
22 another, in the array bind specifically to the reference
23 sequence;
24 (c) hybridizing a target sequence to the array;

25 (d) determining which probes, relative to one
26 another, in the array bind specifically to the target
27 sequence;
28 wherein the relative specific binding of the probes
29 to the reference and the target sequence indicates whether the
30 reference sequence is the same or different from the target
31 sequence.

1 64. The method of claim 63, wherein the reference
2 sequence has a first label and the second reference sequence
3 has a second label different from the first label, and steps
4 (a) and (c) are performed simultaneously.

HIV Chip

1 65. The array of claim 2, wherein the reference sequence
2 is from a human immunodeficiency virus.

1 66. The array of claim 65, wherein the reference
2 sequence is from a reverse transcriptase gene of the human
3 immunodeficiency virus.

1 67. The array of claim 66, wherein the reference
2 sequence is from a protease gene of the human immunodeficiency
3 virus.

1 68. The array of claim 66, wherein the reference
2 sequence is a full-length reverse transcriptase gene.

1 69. The array of claim 68 comprising at least 3200
2 oligonucleotide probes.

1 70. The array of claim 66, wherein the HIV gene is from
2 the BRU HIV strain.

1 71. The array of claim 66, wherein the HIV gene is from
2 the SF2 HIV strain.

1 72. The array of claim 28, wherein the reference
2 sequence is from the coding strand of a reverse transcriptase
3 gene of a human immunodeficiency virus and the second
4 reference sequence is from the noncoding strand of the reverse
5 transcriptase gene.

1 73. The array of claim 28, wherein the first reference
2 sequence is from a reverse transcriptase gene of a human
3 immunodeficiency virus and the second reference sequence
4 comprises a subsequence of the first reference sequence with a
5 substitution of at least one nucleotide.

1 74. The array of claim 73, wherein the substitution
2 confers drug resistance to a human immunodeficiency virus
3 comprising the second reference sequence.

1 75. The array of claim 28, wherein the first and second
2 reference sequences are from a reverse transcriptase gene from
3 first and second strains of a human immunodeficiency virus.

1 76. The array of claim 28, wherein the first reference
2 sequence is from a reverse transcriptase gene of a human
3 immunodeficiency virus and the second reference sequence is
4 from a 16S RNA, or DNA encoding the 16S RNA, from a pathogenic
5 microorganism.

1 77. The array of claim 28, wherein the first reference
2 sequence is from a reverse transcriptase gene of a human
3 immunodeficiency virus and the second reference sequence is
4 from a protease gene of the human immunodeficiency virus.

1 78. The method of claim 54, wherein the reference
2 sequence is from a human immunodeficiency virus.

1 79. The method of claim 78, wherein the reference
2 sequence is from a human immunodeficiency virus and the target
3 sequence is from a second human immunodeficiency virus.

1 80. The method of claim 79, wherein the target sequence
2 has a substituted nucleotide relative to the reference
3 sequence in at least one undetermined position, and the
4 relative specific binding of the probes indicates the location
5 of the position and the nucleotide occupying the position in
6 the target sequence.

1 81. The method of claim 80, wherein the target sequence
2 has a substituted nucleotide relative to the reference
3 sequence in at least one position, the substitution conferring
4 drug resistance to the human immunodeficiency virus, and the
5 relative specific binding of the probes reveals the
6 substitution.

1 82. The method of claim 78, wherein:
2 the hybridizing step comprises hybridizing the
3 target nucleic acid and a second target nucleic acid, the
4 second target sequence being from a reverse transcriptase gene
5 of a third human immunodeficiency virus, to the array; and
6 the determining step comprises determining which
7 probes, relative to one another, in the array bind
8 specifically to the target nucleic acid or the second target
9 nucleic acid, the relative specific binding of the probes
10 indicating whether the target sequence is the same or
11 different from the reference sequence and whether the second
12 target sequence is the same or different from the reference
13 sequence.

1 83. The method of claim 82, wherein the first target
2 sequence has a first label and the second target sequence has
3 a second label different from the first label.

1 84. The method of claim 82, wherein undetermined first
2 and second proportions of the first and second target
3 sequences are hybridized to the array and the specific binding
4 indicates the proportions.

CFTR Chip

1 85. The array of claim 2, wherein the reference sequence
2 is from a CFTR gene.

1 86. The array of claim 85, wherein the reference
2 sequence is exon 10 of a CFTR gene, and said array comprises
3 over 1000 oligonucleotide probes, 10 to 18 nucleotides in
4 length.

1 87. The array of claim 85, wherein said array comprises
2 a set of probes comprising a specific nucleotide sequence
3 selected from the group of sequences comprising:
4 3'-TTTATAXTAG;
5 3'- TTATAGXAGA;
6 3'- TATAGTXGAA;
7 3'- ATAGTAXAAA;
8 3'- TAGTAGXAAC;
9 3'- AGTAGAXACC;
10 3'- GTAGAAXCCA;
11 3'- TAGAAAXCAC; and
12 3'- AGAAACXACA; wherein each set comprises 4 probes,
13 and X is individually A, G, C, and T for each set.

1 88. The array of claim 85, wherein said group of
2 sequences comprises:
3 3'-TTTATAXTAGAAACC;
4 3'- TTATAGXAGAAACCA;
5 3'- TATAGTXGAAACCAC;
6 3'- ATAGTAXAAACCACA;
7 3'- TAGTAGXAACCACAA;
8 3'- AGTAGAXACCACAAA;
9 3'- GTAGAAXCCACAAAG;
10 3'- TAGAAAXCACAAAGG; and
11 3'- AGAAACXACAAAGGA; wherein each set comprises 4
12 probes, and X is individually A, G, C, and T for each set.

1 89. The array of claim 32, wherein the forty first
2 reference sequences are from a CFTR gene.

1 90. The array of claim 89, wherein each of the forty
2 first reference sequences includes a site of a mutation and at
3 least one adjacent nucleotide.

1 91. The array of claim 90, wherein each of the forty
2 first reference sequences comprises at least five contiguous
3 nucleotides from a CFTR gene.

1 92. The array of claim 89, wherein at least one first
2 reference sequence is a from the coding strand of the cystic
3 fibrosis gene and at least one first reference sequence is
4 from the noncoding strand of the CFTR gene.

1 93. An array of oligonucleotide probes immobilized on a
2 solid support, the array comprising at least a group of probes
3 comprising:

4 a wildtype probe exactly complementary to a subsequence
5 of a reference sequence from a cystic fibrosis gene, the
6 segment having at least five interrogation positions
7 corresponding to five contiguous nucleotides in the reference
8 sequence,

9 a first set of three mutant probes, each identical to the
10 wildtype probe, except in a first of the five interrogation
11 positions, which is occupied by a different nucleotide in each
12 of the three mutant probes and the wildtype probe;

13 a second set of three mutant probes, each identical to
14 the wildtype probe, except in a second of the five
15 interrogation positions, which is occupied by a different
16 nucleotide in each of the three mutant probes and the wildtype
17 probe;

18 a third set of three mutant probes, each identical to the
19 wildtype probe, except in a third of the five interrogation
20 positions, which is occupied by a different nucleotide in each
21 of the three mutant probes and the wildtype probe;

22 a fourth set of three mutant probes, each identical to
23 the wildtype probe, except in a fourth of the five
24 interrogation positions, which is occupied by a different

25 nucleotide in each of the three mutant probes and the wildtype
26 probe;

27 a fifth set of three mutant probes, each identical to the
28 wildtype probe, except in a fifth of the five interrogation
29 positions, which is occupied by a different nucleotide in each
30 of the three mutant probes and the wildtype probe.

1 94. The array of claim 93 comprising first and second
2 groups of probes, each group as defined by claim 93, the first
3 group comprising a wildtype probe exactly complementary to a
4 first reference sequence, and the second group comprising a
5 wildtype probe exactly complementary to a second reference
6 sequence, wherein the second reference sequence is a mutated
7 form of the first reference sequence.

1 95. The array of claim 94, wherein the first reference
2 sequence is from a CFTR gene and the second reference sequence
3 is a mutated form of the first reference sequence.

1 96. The method of claim 56, wherein the target sequence
2 and the second target sequence are from heterozygous alleles
3 of a CFTR gene.

P53 Chip

1 97. The array of claim 2, wherein the reference sequence
2 is a sequence from a p53 gene.

1 98. The array of claim 2, wherein the reference sequence
2 is from an hMLH1 gene.

1 99. The array of claim 2, wherein the reference sequence
2 is from an MSH2 gene.

1 100. The array of claim 28, wherein the reference
2 sequence is from a human P53 gene and the second reference
3 sequence is from an hMLH1 gene.

1 101. The array of claim 100, further comprising:

2 ninth, tenth, eleventh and twelfth probe sets,

3 (1) the ninth probe set comprising a plurality of
4 probes, each probe comprising a segment of at least three
5 nucleotides exactly complementary to a subsequence of a third
6 reference sequence, the segment including at least one
7 interrogation position complementary to a corresponding
8 nucleotide in the third reference sequence,

9 (2) the tenth, eleventh and twelfth probe sets,
10 each comprising a corresponding probe for each probe in the
11 ninth probe set, the probes in the tenth, eleventh and twelfth
12 probe sets being identical to a sequence comprising the
13 corresponding probe from the ninth probe set or a subsequence
14 of at least three nucleotides thereof that includes the at
15 least one interrogation position, except that the at least one
16 interrogation position is occupied by a different nucleotide
17 in each of the four corresponding probes from the ninth,
18 tenth, eleventh and twelfth probe sets.

1 102. The array of claim 97, wherein the first probe set
2 has at least 60 interrogation positions corresponding to at 60
3 contiguous nucleotides from exon 6.

1 103. The array of claim 98, wherein the reference
2 sequence is exon 5 of a p53 gene, the probes are 17
3 nucleotides long, and the first set of probes is exactly
4 complementary to the reference sequence, and the at least one
5 interrogation position is at position 7, relative to a 3'-end
6 of each probe, which 3'-end is covalently attached to the
7 substrate.

Mitochondrial Chip

1 104. The array of claim 2, wherein the reference
2 sequence is from a mitochondrial genome.

1 105. The array of claim 104, wherein said reference
2 sequence is a sequence of a D-loop region.

1 106. The array of claim 105, wherein D-loop region is
2 full-length.

1 107. The array of claim 104, wherein said reference
2 sequence is at least 90% of a full-length mitochondrial
3 genome.

1 108. The array of claim 104, wherein the reference
2 sequence is bounded by positions 16280 to 356 of the
3 mitochondrial genome.